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Articles

Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke

J M Wardlaw, C P Warlow, C Counsell

Summary

Background Recent trials of thrombolytic therapy in acute ischaemic stroke have given apparently conflicting results. Only one trial, the National Institute of Neurological Disorders and Stroke trial of tissue plasminogen activator (tPA), suggested that thrombolysis was definitely beneficial. To make sense of these results, we have done a systematic review of all available randomised trials of thrombolysis in acute ischaemic stroke.

Methods From all available completed randomised trials of thrombolytic therapy compared with control in acute ischaemic stroke (with prerandomisation CT), we checked tabular data on deaths during roughly the first 2 weeks, deaths from all causes and functional outcome (disability) at the end of the trial follow-up period, and early symptomatic and fatal intracranial haemorrhages.

Findings 12 trials included 3435 patients, of whom 694 (20%) were dead and 1001 (39%) of 2567 were functionally dependent at the end of follow-up (duration of follow-up varied between trials, but the longest was 6 months). 214 (6%) of the 3435 patients had early symptomatic or fatal intracranial haemorrhages. Thrombolytic therapy was associated with a significant excess of early deaths (91 per 1000 patients treated [95% CI 54–134]), and total deaths (37 per 1000 [20–83]), but there was nevertheless a significant reduction in the number of patients in the combined outcome of dead or dependent (65 fewer per 1000 patients treated [28–107]). There was a substantial and significant excess of symptomatic and fatal intracranial haemorrhages with thrombolysis—which was similar in all recent trials—of about 70 extra symptomatic intracranial haemorrhages per 1000 patients treated (of which 51 per 1000 were fatal). In the cohort of patients randomised within 3 h of stroke, there was a significant reduction in the number of patients who were dead or dependent at the end of follow-up (141 fewer dead or dependent per 1000 patients treated [75–206] and a non-significant increase in the number dead (nine per 1000 treated [−39 to 70]). There was significant heterogeneity between the trials for total deaths at the end of follow-up, which may be partly explained by differences in the use of antithrombotic drugs within the first 24 h of thrombolysis; the variation in severity of strokes included: the time window to thrombolytic treatment; and the dose of thrombolytic drug used. There were no direct comparisons of tPA with streptokinase or urokinase: much of the poor outcome in the streptokinase-treated patients might be explained by the inclusion of more severe strokes, greater use of antithrombotic drugs, higher doses, and the longer time to treatment compared with the trials that used tPA.

Interpretation Thrombolysis requires further testing in large randomised trials because the risks seem substantial, and the benefit uncertain. The time window for effective treatment remains unclear. There is no objective evidence to suggest that tPA is safer than streptokinase; the apparent hazards and benefits may be similar when differences in trial design and baseline variables are accounted for.

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Introduction

Thrombolysis was first tested as a treatment for acute ischaemic stroke nearly 40 years ago.[1] There have since been many case reports and non-randomised studies. However, only six randomised controlled trials (RCTs) in which thrombolysis was compared with control (ie, no thrombolysis) in acute stroke of presumed ischaemic origin (presumed because two of the trials were done before the invention of CT scanning) had been published by 1992.[2] These trials included a total of about 700 patients. Thrombolysis can be reliably assessed only in RCTs because both the intended beneficial effects (reperfusion and neurological improvement) and the feared adverse effects (intracranial haemorrhage and neurological deterioration) can occur spontaneously in patients who have received no treatment for their stroke.

Since 1992, a further eight RCTs have been published, of which five were moderately large, bringing the total number of patients randomised to 3435. Of these five trials, three that tested streptokinase stopped prematurely (owing to excess deaths in the streptokinase-treated group in two,[3,4] and a declining randomisation rate owing to safety worries in the other[5]), and two that tested tissue plasminogen activator (tPA) reached their planned sample size.[6,7] One of these trials showed a statistically significant reduction in poor functional outcome—the National Institute of Neurological Disorders and Stroke trial (NINDS), which tested tPA given within 3 h of the stroke.[6] On the basis of this single trial, the US Food and Drug Administration has recommended the licensing of tPA for use in ischaemic stroke if given within 3 h of onset, and if the patient meets the criteria used to select patients for the NINDS trial. The American Heart Association Guidelines on the treatment of stroke have been revised to include the recommendation that tPA should be used within 3 h of ischaemic stroke,[8] though an

Department of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK (J M Wardlaw FRCR, C P Warlow FRCP, C Counsell MRCP)

Correspondence to: Dr J M Wardlaw, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, Scotland, UK
e-mail: JMW@skull.dcn.ed.ac.uk

	Abe[29]	Atarashi[28]	Ohtomo[31]	Mori[32]	JTSG[33]	Haley[34]
Thrombolytic						
Drug*	Urokinase	Urokinase	Urokinase	tPA	tPA	tPA
Dose	60 000 u/day	240 000 or 6000 u/day	240 000 or 6000 u/day	34 or 51 mg (20 or 30 MIU)	34 mg	0·85 mg/kg
Duration	7 days	7 days	7 days	1 h	1 h	1 h
Control	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Antithrombotic drugs						
Protocol	Avoid for 10 days	Avoid for 10 days	Avoid for 10 days	Avoid for 24 h	Avoid for 24 h	Avoid IV heparin for several hours
Actual amount used	Little	Little	Little	Little	Not known	Little
Patients						
Age limits (years)	>18	>18	>18	18–80	18–80	18–80
Stroke type*	All severities: presumed thrombotic	All except severe neurological deficit; presumed thrombotic	Non-embolic	Carotid territory; angiogram to show occluded cerebral artery	Carotid territory thromboembolic; angiogram to show occluded artery	Any ischaemic stroke (not severe)
Time window‡	2 weeks	<5 days	<5 days	<6 h	<6 h	<3 h
Year of publication	1981	1985	1985	1992	1993	1993
Follow-up	4 weeks†	4 weeks†	4 weeks†	4 weeks	4 weeks	3 months

	Morris[18]	ECASS[3]	MAST-I[4]	NINDS[4]	MAST-E[3]	ASK[4]
Thrombolytic						
Drug*	Streptokinase	tPA	Streptokinase	tPA	Streptokinase	Streptokinase
Dose	1·5 MU	1·1 mg/kg (max 100 mg)	1·5 MU	0·9 mg/kg (max 90 mg)	1·5 MU	1·5 MU
Duration	1 h	1 h	1 h	1 h	1 h	1 h
Control	Placebo	Placebo	Open	Placebo	Placebo	Placebo
Antithrombotic drugs						
Protocol	Avoid	No aspirin or IV heparin but SC heparin allowed <24 h; thereafter any antithrombotic	Randomised between immediate aspirin *vs* avoid or 10 days: avoid others	Avoid for 24 h	Not specified: at discretion of attending physician	All to receive 300 mg aspirin within 4 h of randomisation
Actual amount used	Little	Not known	50% (aspirin groups)	Not known	30% <24h 60% <10 days	Not known
Patients						
Age limits (years)	40–80	18–80	>18	18–80	>18	18–85
Stroke type*	Carotid territory	Carotid territory (large)	Any except if in coma	Any except very mild and very severe strict BP control:	Large carotid/MCA territory stroke	Any ischaemic stroke (not mild)
Time window	6 h	6 h	6 h	3 h	6 h	4 h
Year of publication	1995	1995	1995	1995	1996	1996
Follow-up	3 months	3 months	6 months	3 months	6 months	3 months

IV=intravenous; SC=subcutaneous; MCA=middle cerebral artery. *All trials used CT to exclude haemorrhage (and visible infarction in ECASS'). †Follow-up was at 4 weeks from start of treatment, which might be up to 14 days after stroke; in other trials, it was at time shown from stroke. ‡Time to randomisation from stroke onset.

Table: **Design characteristics of trials and other key factors**

ad hoc European Committee was more cautious.[9] Although tPA has been regarded favourably, streptokinase has been branded dangerous and not worth testing further.[10,11] However, recommendations based on the results of individual trials can be misleading (especially if these trials are not particularly large) because of the risk of both false-positive and false-negative results.[12] The purpose of this systematic review, therefore, is to present all available evidence from the RCTs of thrombolysis to enable more informed decision-making.

Methods

This paper summarises a systematic review we produced for the Cochrane Stroke Review Group, which is periodically updated and published in the Cochrane Library.[13] We have tried to identify all randomised controlled trials of a thrombolytic agent compared with control published in any language by electronic searching of Medline, of Embase, and of the Ottawa Stroke Trials Registry; hand-searching abstracts of major stroke conferences since 1990, several Japanese, Chinese, and all major English-language stroke, neurology, and general medicine journals since 1980; attendance at the Second, Third, and Fourth International Thrombolysis in Acute Ischaemic Stroke Symposia; contact with other interested trialists; written correspondence with all pharmaceutical companies listed in the *British National Formulary* and the *Monthly Index of Medical Specialties* (and their world-wide associates) to check for unpublished data; and the checking of references cited in other publications about thrombolysis.[14]

Trials were included only if they were: first, truly randomised in a way that precluded prior knowledge of the next treatment allocation (eg, alternation would not suffice); second, if they were unconfounded, such that one group differed from another only in the treatment of interest (we included the streptokinase-plus-aspirin *vs* aspirin groups of the MAST-Italy trial[3] separately, since this comparison is unconfounded for streptokinase and provides the only randomised evidence of a potentially important interaction between streptokinase and aspirin); third, if they were analysed on an intention-to-treat basis (or if unpublished information on outcome could be obtained on all randomised patients, thus allowing an intention-to-treat analysis to be done); and, fourth, if they included only definite ischaemic stroke (ie, a CT or MR scan was mandatory before randomisation to exclude intracranial haemorrhage or other non-stroke disorders).

Data extracted from each included trial were: the number of patients in the treated and control groups who had died from any cause (within about the first 2 weeks and by the end of the trial follow-up period); who were dependent on others in activities of daily living by the end of follow-up; and who had developed symptomatic or fatal intracranial haemorrhage in the acute stage.

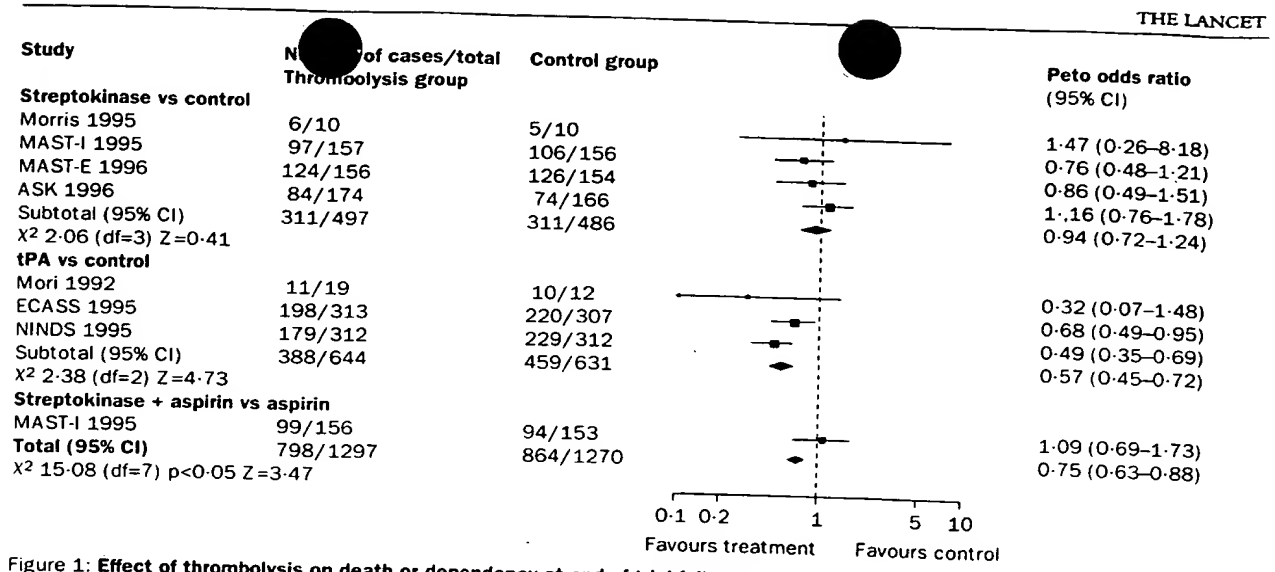


Figure 1: **Effect of thrombolysis on death or dependency at end of trial follow-up**
χ^2 refers to test for heterogeneity across different trials. Z is test statistic for odds ratio. Odds ratios for individual trials (area of square proportional to amount of information contributed) and for subtotals and total (diamond=odds ratio and 95% CI).

These data were extracted from published and orally presented data by JMW. If any relevant data were missing, or ambiguous, we wrote to the principal investigators and have verification for all but the NINDS trial[9] and the small trials by Haley and colleagues[14] and Morris and colleagues.[15] We were unable to obtain data on individual patients for the majority of trials, so our analyses are from tabular data. Poor outcome was defined as death or dependency as measured by the Rankin or Barthel scales at the end of follow-up. The composite outcome of death and dependency is the most important outcome, since the aim of treatment should be not only to prevent death, but also to prevent serious disability in survivors. Intracranial haemorrhage was defined as haemorrhage into the infarct or elsewhere within the cranial cavity (subarachnoid or subdural space, or into the brain parenchyma outside the infarct) after randomisation, confirmed by CT (or MR) scan or necropsy. Symptomatic intracranial haemorrhage was defined as neurological deterioration associated temporally with the appearance of new intracranial haemorrhage on the CT or MR scan. Fatal intracranial haemorrhage was defined as death that apparently resulted directly from intracranial haemorrhage confirmed on CT scan, MRI, or at necropsy.

Both proportional and absolute risk reductions were calculated for each outcome. Additional subgroup analyses were planned to examine the effect of the time to treatment (≤ 3 h *vs* ≥ 3 h), use of antithrombotic drugs, dose of thrombolytic drug, age of patient, and stroke severity if data were available. Heterogeneity between trial results was assessed with a standard χ^2 test. The results are reported as odds ratios (ie, the ratio of the odds of an unfavourable outcome among treatment-allocated patients to the corresponding odds among controls), which were calculated by the Peto fixed-effects method.[16] An odds ratio of 1 indicates no difference between treatment and control; less than 1 favours treatment; and greater than 1 suggests that treatment is hazardous. A practical description of the philosophy behind the use of odds ratios is given elsewhere.[17] If heterogeneity was found between the results of different trials, the contribution of each trial to the heterogeneity was calculated.[16] There were insufficient trials for us to do meaningful multivariate analyses to assess the effects of various trial characteristics on the results—eg, type or dose of thrombolytic drug, use of antiplatelet therapy, delay to treatment, or duration of follow-up. However, we did assess the effect of these trial characteristics on the results in a series of univariate comparisons, though such comparisons between trials are crude and can only be regarded as hypothesis-generating.

Results

12 trials met the inclusion criteria with a total of 3435 patients, but not all of these trials provided data for every outcome of interest. Four other completed RCTs were excluded: in one, many patients were lost to follow-up, and we could not obtain any outcome information to allow intention-to-treat analysis to be done (101 patients were randomised, but data were available on only 71);[19] another RCT was very small and was stopped prematurely after randomisation of only four patients owing to the impracticability of intra-arterial thrombolysis.[20] The remaining two RCTs were done in the 1960s when CT scanning was not available, and consequently cannot be guaranteed to have included only patients with ischaemic stroke.[21,22] Two further RCTs that stopped prematurely have yet to be published: Thrombolytic Therapy in Acute Thrombotic Thromboembolic Stroke (TTATTS), which was completed in 1992 (though the company, Genentech, had not released any data until 1997), and a small trial in Hong Kong that is thought to have included a few patients only. Three apparently randomised controlled trials have been done in China, one with lumbrokinase (a thrombolytic agent extracted from earthworms), and two with urokinase[23-25] (on which we are trying to obtain more information). A further five trials at least are still continuing, and some may finish within the next year (AUST,[26] Genentech, PROACT,[27] the EMS Bridging trial,[28] and ECASS II), but none of these are likely to randomise more than 800 patients. Thus, the included 12 trials are likely to represent the best evidence for some time on thrombolytic therapy in acute ischaemic stroke.

The principal features of each included trial are given in the table. Two trials stopped prematurely (MAST-E[3] and ASK[4]) because of excess deaths in the thrombolysis-treated group, and a third (MAST-I[5]) stopped after randomising only about a third of the intended number of participants owing to safety concerns. All of the 12 included trials gave the thrombolytic drug by intravenous infusion. Three used urokinase,[29-31] four streptokinase,[3-5] and five tPA.[6,7,14,32,33] 11 were placebo-controlled, whereas one (MAST-I)[5] randomised between streptokinase alone, streptokinase plus aspirin, aspirin alone, and "open"

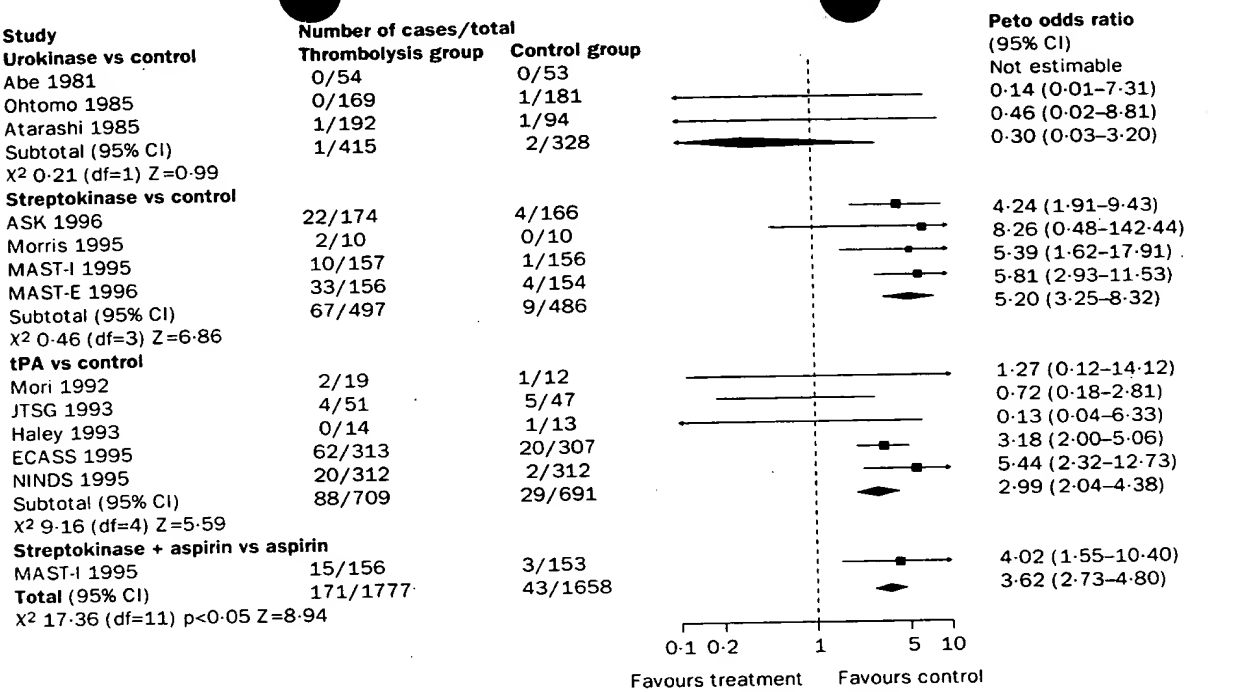


Figure 2: **Effect of thrombolysis on symptomatic intracranial haemorrhage (fatal and non fatal) within about first 2 weeks of treatment**

control (though both the physician and patient knew whether or not thrombolytic therapy had been administered, at 6 months the person assessing outcome was blind to treatment allocation).

Six trials roughly used the same dose of thrombolytic as that used to treat acute myocardial infarction in Europe and the USA: 1·5 MU streptokinase over 1 h intravenously,[3–5,15] or 0·85–1·1 mg/kg tPA over 1 h intravenously to a maximum dose of 100 mg.[6,7,17] Two Japanese trials used about half or less of the dose used to treat acute myocardial infarction in Europe and the USA: 34 or 51 mg tPA over 1 h intravenously.[32,33] Three other Japanese trials used less than the equivalent dose for the treatment of acute myocardial infarction, but gave repeated doses: 6 or 24×10^4 units urokinase per day intravenously for 7 days.[29–31]

The time from stroke onset to symptoms was a major eligibility criterion in the trials: two trials randomised within 3 h of stroke onset,[6,14] one within 4 h,[4] six within 6 h,[3,5,7,15,32,33] two within 5 days,[30,31] and one within 2 weeks.[29]

Antithrombotic drugs (aspirin and heparin) were forbidden for the first 10 days in six trials[5,27–31] and for the first 24 h in two trials;[6,13] they were given to some patients within the first 24 h at the discretion of the attending physician (though the exact number of patients, and exactly how much they received is not known) in three trials,[3,7,14] and were given, according to protocol, to all patients within the first 24 h in two trials (ASK[4] and the streptokinase plus aspirin group of MAST-I[5]). The target study population was patients with large infarcts in the carotid territory only for three trials,[3,7,14] patients with cardioembolic strokes and angiographic evidence of occlusion of the internal carotid or middle cerebral artery for two,[30,31] patients with stroke of any severity (except for those who were comatose), lacunar or cortical, carotid-artery or vertebral-artery territory for four,[4–6] and patients with presumed non-cardioembolic ischaemic stroke for three.[27–29] Six trials excluded patients older than 80,[6,7,13,14,30,31] one trial excluded patients older than 85,[4] and five had no upper age limit.[3,5,27–29]

There are likely to be other important differences between the trials in terms of the patients' baseline characteristics, indicated crudely by the substantial differences in the case-fatality rates in the control groups between the trials. These rates varied from 2%[29] to 38%.[3] For example, in MAST-E,[3] about half the patients were drowsy or comatose at randomisation, and 38% of patients in the control group had died by 6 months; whereas in the NINDS trial,[6] only about 20% of patients had the "maximum" NIHSS score at randomisation, and only 20% of patients in the control group had died by 3 months.

Effects on functional outcome

Seven trials assessed poor functional outcome, four with the Rankin scale (in MAST-I,[5] and MAST-E[3] ≥3 on the modified Rankin scale; in ECASS[7] and NINDS[6] ≥2 on the modified Rankin scale), and three used the Barthel Index (Mori,[32] ASK,[4] Morris:[15] ≤60 on a scale on which 100 indicated no symptoms). The trials by Abe,[29] Atarashi,[30] and Ohtomo[31] used a global improvement rating, which measures change in neurological status, not functional outcome. The JTSG[33] has published results only with the hemispheric stroke scale, though the Barthel was measured. The final follow-up was at 1 month in two trials,[15,32] at 3 months in three,[4,6,7] and at 6 months in two;[3,5] in all trials, the timing of follow-up was the same in the treated and control groups. Data from the trial by Haley and colleagues[14] are incomplete (three of 27 patients are alive, but their functional status is unknown).

Among the 1297 patients allocated thrombolysis, 798

Study	Number of cases/total		Peto odds ratio
Urokinase vs control	**Thrombolysis group**	**Control group**	(95% CI)
Abe 1981	1/54	1/53	0·98 (0·06–15·90)
Ohtomo 1985	3/169	6/181	0·54 (0·14–2·03)
Atarashi 1985	7/192	4/94	0·85 (0·24–3·05)
Subtotal (95% CI)	11/415	11/328	0·71 (0·30–1·70)
X^2 0·29 (df=2) Z=0·78			
Streptokinase vs control			
Morris 1995	3/10	3/10	1·00 (0·15–6·45)
MAST-I 1995	44/157	45/156	0·96 (0·59–1·57)
MAST-E 1996	73/156	59/154	1·41 (0·90–2·22)
ASK 1996	63/174	34/166	2·16 (1·35–3·45)
Subtotal (95% CI)	183/497	141/486	1·43 (1·10–1·88)
X^2 5·61 (df=3) Z=2·64			
tPA vs control			
Mori 1992	2/19	2/12	0·59 (0·07–4·91)
JTSG 1993	3/51	4/47	0·68 (0·15–3·12)
Haley 1993	1/14	3/13	0·30 (0·04–2·39)
ECASS 1995	69/313	48/307	1·52 (1·02–2·27)
NINDS 1995	54/312	64/312	0·81 (0·54–1·21)
Subtotal (95% CI)	129/709	121/691	1·06 (0·80–1·39)
X^2 6·84 (df=4) Z=0·39			
Streptokinase + aspirin vs aspirin			
MAST-I 1995	68/156	30/153	3·02 (1·87–4·87)
Total (95% CI)	391/1777	303/1658	1·36 (1·14–1·62)
X^2 28·96 (df=12) p<0·01 Z=3·46			

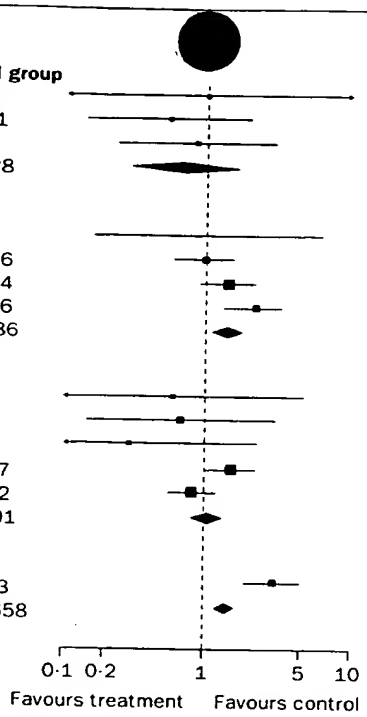


Figure 3: **Effect of thrombolysis on total case fatality (early and late) at end of trial follow-up**

(61·5%) were dead or dependent on others in activities of daily living, compared with 864 (68·0%) of 1270 allocated control. This 6·5% absolute reduction in poor outcome is significant (odds ratio 0·75 [95% CI 0·63–0·88], 2p=0·0005), and corresponds to about 65 fewer dead or dependent patients per 1000 treated with thrombolysis (95% CI 28–107), and would be clinically important if confirmed in larger trials.

Effects on early case fatality

Seven trials assessed fatality within about the first 2 weeks of the stroke,[3-7,14,15] but the precise data from the NINDS trial[6] are not available, since only a survival curve was published from which it is not possible to extract the exact numbers reliably. In the six other trials, there was a substantial excess of deaths in the thrombolysis-treated patients: 207 (20·9%) of 989 in the thrombolysis-treated patients compared with 113 (11·8%) of 961 in the control group. This 9·1% increase in early death with thrombolysis is highly significant, with an odds ratio indicating a twofold increase (odds ratio 1·99[1·56–2·53], 2p<0·0001)—ie, an extra 91 deaths (54–134) in the first 2 weeks per 1000 patients treated with thrombolysis.

Effects on intracranial haemorrhage

Thrombolysis substantially increased symptomatic and fatal intracranial haemorrhage (most occurring in about the first 2 weeks) in all the recent trials, including the NINDS trial (figure 2).[6] Among the 1777 thrombolysis-treated patients there were 171 (9·6%) symptomatic intracranial haemorrhages, of which 92 (6·2%) of 1484 were fatal. In the control group there were 43 (2·6%) symptomatic haemorrhages among 1658 patients, and 15 (1·1%) fatal intracranial haemorrhages among 1365 patients. There was, therefore, an absolute excess with thrombolysis of 7% symptomatic (odds ratio 3·62 [2·73–4·80], 2p<0·00001), and 5·1% fatal (4·44 [2·66–7·4]) intracranial haemorrhages; or an extra 70 per 1000 symptomatic intracranial haemorrhages—of which 51 per 100 were fatal.

Effect on total (early and late) case fatality

All 12 trials recorded the number of deaths at the end of the follow-up period. Of 1777 patients given thrombolysis, 391 (22%) were dead, compared with 303 (18·3%) of 1658 controls (figure 3). This 3·7% increase in late case fatality is also significant (odds ratio 1·36 [1·14–1·62], 2p=0·0005), and is consistent with an extra 37 deaths (20–83) per 1000 patients treated with thrombolysis. In the four trials (ASK,[4] ECASS,[7] MAST-E,[3] MAST-I[5]) that provided data for both early and late fatality, there was a non-significant trend for the excess of deaths with thrombolysis to decrease with time (early case fatality odds ratio 2·07, late case fatality 1·67; 2p=0·18).

Heterogeneity between trial results

There was substantial heterogeneity for all outcomes, except those for symptomatic intracranial haemorrhage. The potential causes for this heterogeneity must be investigated further, ideally with data for individual patients—to which, unfortunately, we did not have access. However, we did undertake several further exploratory analyses to examine possible explanations for the heterogeneity (given in methods). We concentrated on the outcome of case fatality at the end of follow-up, since this outcome had the most data and showed the greatest heterogeneity (χ^2 28·96, df 12, p<0·01).

Analyses showed that the heterogeneity was largely due to three trials: ASK[4] (odds ratio 2·16), MAST-I[5] streptokinase plus aspirin group (3·02), and NINDS[6] (0·81). We also analysed which trial characteristics might have explained the heterogeneity.

Case fatality	Number of cases/total		Peto odds ratio
Streptokinase vs control	**Thrombolysis group**	**Control group**	(95% CI)
MAST-I 1995	7/35	23/57	0·40 (0·16–0·98)
MAST-E 1996	18/26	4/21	7·19 (2·30–22·48)
ASK 1996	11/41	7/29	1·15 (0·39–3·38)
Subtotal (95% CI)	36/102	34/107	1·18 (0·66–2·14)
X^2 15·29 (df=2) Z=0·56			
tPA vs control			
Haley 1993	1/14	3/13	0·30 (0·04–2·39)
ECASS 1995	13/49	8/38	1·34 (0·50–3·60)
NINDS 1995	54/312	64/312	0·81 (0·54–1·21)
Subtotal (95% CI)	68/375	75/363	0·84 (0·59–1·22)
X^2 1·86 (df=2) Z=0·91			
Streptokinase + aspirin vs aspirin			
MAST-I 1995	19/44	8/46	3·37 (1·37–8·26)
Total (95% CI)	123/521	117/516	1·06 (0·79–1·43)
X^2 25·17 (df=6) p<0·001 Z=0·41			

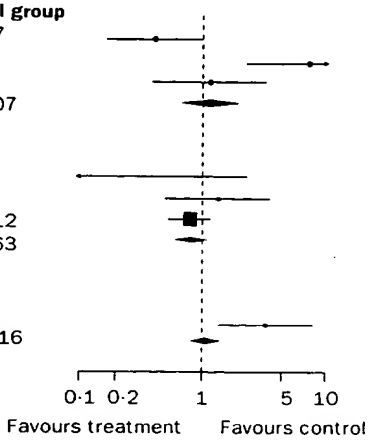


Figure 4: **Effect of thrombolysis on case fatality (a) and death or dependence (b, over page) at end of follow-up in cohort of patients randomly assigned within 3 h of stroke onset**

Time to randomisation

There was evidence of a difference in case fatality between the results of trials that restricted entry to within 3 h of stroke and those with longer time-windows (odds ratio 0·78 *vs* 1·56, 2p=0·01). We obtained verified tabular data for all patients randomised within 3 h from the four most recent trials with longer time-windows (ASK,[4] MAST-E,[3] ECASS,[7] MAST-I[5]). Analysis of all patients randomised within 3 h (including the NINDS trial[6]) showed that there was no longer a significant excess of deaths associated with thrombolysis at the end of follow-up, but that there was still significant heterogeneity among trials (figure 4), again, largely due to three trials (MAST-E,[3] odds ratio 7·19; MAST-I[5] streptokinase without aspirin arm, 0·4; MAST-I[5] streptokinase with aspirin, 3·37). This analysis suggests that time to randomisation was not the sole cause of heterogeneity. For the four recent trials with time-windows greater than 3 h[3-5,7] we were able to compare directly the results from patients randomised within 3 h and results for those randomised at 3–4 h (ASK[4]) or 3–6 h (MAST-E,[3] MAST-I,[5] ECASS[7]) from stroke onset. There was no clear evidence of a difference between the two groups (randomised within 3 h, odds ratio 1·56, randomised after 3 but under 6 h, odds ratio 1·72, 2p=0·7). When analysis of death and dependency was restricted to patients randomised within 3 h, there was no evidence of heterogeneity (χ^2 4·06, df=5, p>0·2), and the result was similar to that for death or dependency overall (odds ratio 0·55; figure 4). Exclusion of the NINDS study, which contributed more than 50% of data within 3 h, did not substantially alter the conclusions.

Type and dosage of thrombolytic agent

There was no clear evidence of differences in total case fatality between trials with urokinase (0·71), streptokinase (1·43), or tPA (1·06), or between trials that used low[32,33] and high doses of tPA[6,7,14] (0·64 *vs* 1·08, 2p=0·4). There were too few data in trials that directly compared two different doses of urokinase for us to draw reliable conclusions.[30,31]

Concomitant use of antiplatelet agents

There was strong evidence from MAST-I[5] of an important interaction between aspirin and streptokinase such that the combination seemed particularly dangerous (odds ratio for total death with streptokinase was 0·96 without aspirin, and 3·02 with aspirin, 2p=0·001). The excess of deaths began 2 days after onset and increased thereafter due to deaths from all causes (cerebral haemorrhage, massive oedema in the infarct, cardiac and other systemic causes[34]). However, this analysis was based on only 600 patients and was confounded by imbalances in baseline prognosis. Two other trials permitted early use of aspirin.[3,4] Combining the three trials that permitted early use of aspirin did suggest to us that the odds of death was higher than in the remaining trials that tended to avoid early aspirin (odds ratio 2·06 *vs* 1·01, 2p<0·0001).

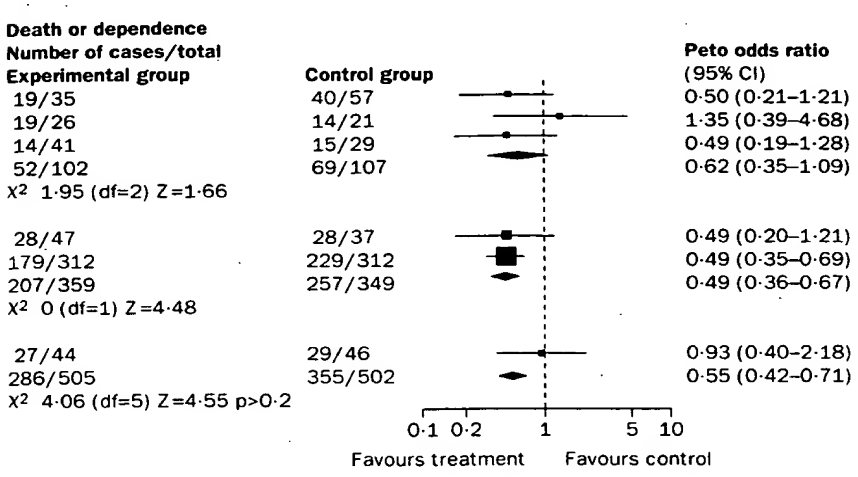
Baseline prognosis

Analysis of MAST-I[5] had suggested that patients with poor prognosis at time of treatment (mainly because of a large stroke) had hazard but no benefit from thrombolysis (absolute increase of 7% in the number dead or dependent at 6 months), whereas patients with a better prognosis (ie, small infarct) had some hazard but more benefit (absolute reduction of 12% in the number dead or dependent at 6 months).[35] This subgroup analysis must be interpreted with extreme caution because it was based on very small numbers, and neither result was significant. Analysis of the effects of baseline prognosis on the results of our meta-analysis is difficult because we did not have data for individual patients for the other trials. A plot of the risk of death in the treatment group compared with that in the control group[36] did not show that trials with particularly high risks in the control group were the cause of the heterogeneity. The three trials that contributed most to the heterogeneity all had similar and intermediate risks of death (20–21%) in the control group.[4-6] Similarly, there was no significant difference between the results of trials that included patients with lacunar strokes (which have the best prognosis) and trials that excluded them (odds ratio 1·34 *vs* 1·39, 2p=0·8).

Duration of follow-up

The odds of case fatality did not differ significantly between trials with 1, 3, or 6 months follow-up (odds ratio 0·69, 1·29, and 1·6, respectively).

Several other variables might partly explain the degree



of heterogeneity (eg, how well blood pressure was controlled during and after thrombolysis), but we did not have access to data that allowed us to examine these variables.

Discussion

Thrombolytic therapy in acute ischaemic stroke evidently carries substantial risk; but the available data also hint at worthwhile benefits. There was marked heterogeneity between trials for most of the outcomes we assessed. Thus, interpretation of a single summary odds ratio or absolute risk reduction across all trials is difficult, since the actual treatment effect may vary according to the type of thrombolysis used, and the type of patient treated. However, for most patients included in the trials, the thrombolytic regimens increased the risk of death, but reduced the risk of the combined outcome of death or dependency.

The question of which patients are at greatest risk of hazard or of benefit from treatment is more difficult. There is some evidence that earlier treatment (within 3 h) is better than late treatment, and that coadministration of antiplatelet therapy is harmful; but even these analyses are limited. Differences that depend on baseline risk, agent, and dose, remain purely speculative. There are no comparisons of different thrombolytic drugs. The poorer outcomes in the trials with streptokinase than in those with tPA can be accounted for by factors other than the agent used. Despite the inclusion of all available evidence, the numbers are far too small for us to draw anything other than broad conclusions. In addition to small numbers, there were other difficulties related to methods, such as missing data on certain outcome measures from some trials, the various measures of dependency, differences in the duration of follow-up, and the risk that unblinding may lead to bias (it is difficult to conceal from investigators the biological effects—such as prolonged bleeding times—of thrombolytic drugs in the doses used). If future meta-analyses of individual data from all trials, as well as from new trials, could sort out the possible markers of hazard suggested here (as well as others that we have not been able to address), thrombolysis could turn out to be a worthwhile treatment for clearly defined patients.

The number of patients available for inclusion in this analysis (3435) is tiny compared with the 4·4 million patients who die of a stroke each year worldwide.[37] Also, l[illegible] trials were needed to co[illegible]nce clinicians of the benefit of thrombolysis in myocardial infarction (about 50 000 patients).[17] On currently available evidence, therefore, it is difficult to justify the routine use of thrombolysis outside randomised trials. We must bear in mind that the NINDS trial,[6] which led the US Food and Drug Administration to grant a licence for the use of tPA within 3 h of stroke, took about 6 years to randomise 624 patients between 45 expert centres (about three patients per centre per year)—a tiny fraction of the total number of stroke patients seen in those centres in that time. This statistic shows just how difficult it is to treat stroke patients quickly. Given the potential for substantial hazard shown in other trials, generalisation of the NINDS[6] trial results to most stroke patients in most hospitals would be wrong. In many parts of the world, including the USA, most stroke patients reach hospital long after 3 h or even 6 h and may not have a CT scan to exclude intracranial haemorrhage until even later. If this situation is to change, family doctors, emergency services, clinicians, and hospital managers will need highly persuasive evidence that the benefit is worthwhile. Currently, that weight of evidence does not exist. We cannot expect or prescribe, therefore, a huge change in the management of stroke patients.

Several important issues must be addressed in future trials, including dose of drug (there are no substantial randomised comparisons, and none of streptokinase); which drug (tPA, streptokinase, urokinase, lumbrokinase, &c); what to do with antithrombotic medication (ie, the course of action if patients are taking aspirin at the time of the stroke, and when to start it after thrombolysis); which patients are safe to treat and which should avoid thrombolysis; how to manage blood pressure within the first few hours of thrombolytic treatment; and what the true time-window is to successful treatment. The MAST-I[5] streptokinase-only group suggested that there might be benefit up to 6 h after onset, and there is little evidence of what might happen in patients randomised, say, up to 12 h after onset. In addition, some trials (ECASS,[7] in particular) suggested that other factors, such as the presence of a visible infarct on the CT scan at randomisation, were associated with increased risk, though these signs on CT may be too difficult for non-specialist doctors to recognise.

To answer these questions, more information from larger trials is required. We need accurate results soon, because the benefits would be highly worthwhile if they are similar to those suggested by this review. Failure to recognise the benefit of thrombolysis in acute myocardial infarction has undoubtedly resulted in tens of thousands of unnecessary cardiac deaths over the years. There was clear evidence of benefit as far back as 1973,[38] but the benefit was not recognised and proven in large trials until the late 1980s. Stroke is also common and there is so far no substantially effective treatment, with the exception of a small effect of aspirin.[39] As a matter of urgency, thrombolysis must therefore be tested more thoroughly.

There has been some d[redacted]as to whether the possible benefit of thrombolysis in reducing dependency justifies the early hazard. More conclusive evidence is clearly needed to assess the true risk/benefit ratio. Some claim that patients would rather die of the stroke than survive disabled,[40] but that is a matter for the individual. Moreover, patients need accurate information to make that decision. Suffice to say that most medical interventions have hazard even if we find it easier to see only the benefit—most surgical operations, for example, and many drugs. We need to define and quantify the risks and benefits of thrombolysis much more clearly before it finds its place in the treatment of acute ischaemic stroke.

Contributors

J M Wardlaw was responsible for literature searching, contact with principal investigators (particularly in Japan), journal searching, extraction of data, verification of extracted data, obtaining additional unpublished data from principal investigators, and analysis of data; she also wrote the initial draft of the paper. C P Warlow was responsible for additional contact with principal investigators, ensuring quality of the study methods, interpretation of the data in the context of the world-wide problem of stroke, editing of the manuscript, and steering of the Stroke Review Group of the Cochrane Collaboration from which this review arose. Dr Carl Counsell was responsible for additional data analysis, looking at reasons for heterogeneity, and ensuring that we had not overlooked any trials; he also wrote part of the results section.

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